REMARKS

The present is a Response to the Office Action mailed on October 29, 2009.

In paragraphs 3-22 of the Office Action the Examiner rejected claims 1-16 under 35 U.S.C. §103(a) as being obvious over CAB8-Computer Applications in Biotechnology, June 25-27, 2001 (hereinafter "Cornelissen") in view of Biotechnology and Bioengineering, vol. 34, pp 592-599 (1989) (hereinafter Major), and U.S. Published Application No. 2002/0138454 A1 (hereinafter Gruenberg), and further in view of United States Patent No. 6,402,941 (hereinafter Lucido) and United States Patent No. 6,599,735 (hereinafter Bartok).

Reconsideration is requested.

Claim 1 recites a novel method for biotechnologically producing valuable products using a system of feed receptacles, a bioreactor, pumps, a cross flow filtration unit and at least two harvest receptacles, one for storing filtered permeate and a second for removing cell-contaminated medium. Claim 1 further recites that the method measures the cell concentration of the bioreactor by use of the control unit (6), an analytical system (27), a sensor (28) for measuring cell concentration, an analyzer (41), a first regulator (42), and a first reference operator (43), and then adjusts the cell concentration to a predetermined level by moving cell-contaminated medium from the bioreactor (1) to the second harvest receptacle (18) through the use of a harvest pump (20). Claim 1 further recites a second regulator (44) which receives a signal from a weighing device (22) which measures the weight of the bioreactor (1), and wherein said second regulator (44) compares the weight of said bioreactor (1) with a desired weight stored in a second reference operator (45), and based on the comparison of the measured weight and the desired weight said second regulator (44) sends a control signal to an upstream feed pump (8), which in turn sends medium to the bioreactor (1) from an upstream medium containing feed receptacle (2).

In paragraph 12 of the Office Action the Examiner compares the weighing device in Cornelissen to the system for measuring and readjusting nutrient medium in the bioreactor of the present invention. Applicants submit that the disclosure in Cornelissen does not teach the elements currently recited in claim 1. Specifically the weighing device in Cornelissen is connected to a pump on the ***downstream*** side of the bioreactor, wherein

the ***downstream*** pump connects a product harvest receptacle and a microfiltration device, both of which are also on the ***downstream*** side of the bioreactor. This disclosure teaches away from the presently claimed invention where the weighing device is connected to an ***upstream*** feed pump connected to an ***upstream*** medium containing feed receptacle. More specifically, the ***downstream*** pump in Cornelissen is removing filtrate from the bioreactor, whereas the ***upstream*** pump in the present invention is adding medium to the bioreactor. These are wholly different elements and processes.

The Examiner has stated in paragraph 7 of the Office Action that the primary reference, Cornelissen does not teach a second harvest vessel for removing cell-contaminated medium. The Examiner has also stated in paragraph 10 of the Office Action that Cornelissen does not disclose a method for measuring the cell concentration in the bioreactor. Applicants submit that the Examiner is correct in highlighting these deficiencies in the primary reference and further submit that neither Cornelissen, nor the secondary references, disclose or suggest the recited method, including each and every element used to measure and readjust the cell concentration in the bioreactor and/or weight the bioreactor and add additional nutrient feed.

To alleviate the deficiencies in Cornelissen, the Examiner has cited four additional documents. The first reference Major, discloses a continuous fermenter for producing lactate. The only disclosure in the journal article cited by the Examiner is a simple figure on page 593, and one paragraph on page 594, which briefly describes removing a "whole culture" from a fermenter. A person skilled in the art would not combine Cornelissen and Major as suggested by the Examiner because Cornelissen already describes a process for removing waste from the bioreactor. Specifically, Figure 1, on page 2 of Cornelissen demonstrates a procedure in which the harvest receptacle, which contains filtered permeate, is subjected to an additional ultra-filtration process and waste is removed from the first harvest receptacle. Therefore, because Cornelissen already provides instructions on removing waste from the filtrate a person skilled in the art would not look for additional waste removal steps as disclosed in Major and would not seek to combine the two references.

Moreover, neither reference discloses or suggests the need to measure cell concentration, a system for cell concentration measurement or a system for readjusting cell concentration as recited in the pending claims. Additionally, neither Major nor

Cornelissen teach the use an ***upstream*** regulator connected to a device for weighing the bioreactor, wherein the regulator is further connected to a reference operator to compare the measured weight with the reference weight, and wherein the regulator is further connected to an ***upstream*** feed pump which in turn is connected to an ***upstream feed receptacle***, which can supply nutrient medium to replenish the bioreactor.

Next the Examiner points to Gruenberg and Lucido in an attempt to alleviate the deficiency in Cornelissen and Major, namely, the lack of instruction regarding the method for measuring and controlling the cell concentration and total reactants in the bioreactor. As disclosed above, claim 1 recites a method for measuring cell concentration of the bioreactor using a control unit (6), an analytical system (27), a sensor (28) for measuring cell concentration, an analyzer (41), a first regulator (42), and a first reference operator (43), wherein the cell-contaminated medium is removed from the bioreactor (1) to the second harvest receptacle (18) through the use of a harvest pump (20). None of these claim elements are disclosed in the cited prior art in the combination recited in claim 1.

While Gruenberg teaches a device for measuring the weight of the nutrient feed or the weight of the bioreactor, it does not teach a method of measuring the cell concentration in the bioreactor and a method for regulating the cell concentration of the bioreactor. Gruenberg teaches the use of a Mettler balance in combination with a peristaltic pump and a software solution which may be connected with the bioreactor or to nutrient medium containers. *See* Paragraphs 0060, 0109 and 0121. However, these elements do not render obvious each and every element of the claim 1, namely, the control unit (6), an analytical system (27), sensor (28) for measuring cell concentration, analyzer (41), first regulator (42), and first reference operator (43) as recited in claim 1. The Examiner has only generally described processes in Gruenberg and extrapolated their relevance to the specifically recited elements in the present claims. Further, since the elements disclosed in Gruenberg, relate to a method for measuring nutrient feed or reactor weight, they have no relation to the specific measuring and removing of cell concentration recited in claim 1. *See* Gruenberg at paragraphs 0019, 0064, 0109, 0121-0122.

More specifically, the teaching in Gruenberg never discloses that the device for measuring the weight of the bioreactor is directly connected to anything but a discharge

pump (not a feed pump) and that while the nutrient feed receptacles are connected to a balance, software and pumps, they are not directly connected to a device for measuring the weight of the bioreactor and cannot be used to remove cell-contaminated medium from the bioreactor to a second harvest receptacle. Therefore the claim elements related to the first regulator (42) and second regulator (44) are not rendered obvious by the disclosure in Gruenberg.

As discussed above in relation to Cornelissen, Gruenberg does not disclose a second harvest receptacle for removing cell contaminate and therefore the claim elements related to the first regulator (42) and the removal of cell contaminate from the bioreactor cannot be rendered obvious by the disclosure in Gruenberg. Furthermore, Applicants submit that Major could not be combined with Gruenberg because the system in Gruenberg appears to be remove the entire fermented product from the bioreactor. Therefore, Major cannot be combined with Gruenberg because as best as can be determined it discloses a procedure in which the filtration, if it occurs, happens after the final product has already been removed from the bioreactor. This is not the method disclosed in the present claims in which the medium is removed from the bioreactor, filtered and stored; retentate is returned to the bioreactor, and simultaneously cell-contaminated product can be separately removed from the bioreactor. Because the disclosure in Gruenberg appears to remove fermented medium as a whole, it is incompatible with Major, and does not render the present claims obvious.

Lucido discloses an apparatus for biological treatment of environmental contaminants and waste. The teachings highlighted by the Examiner in Lucido are contained in col. 8, lines 30-35, which teach that an optical sensor can be used to measure turbidity in the bioreactors, and that a higher turbidity can indicate a higher viable cell concentration. *See id.* Applicants submit that the above teaching does not render obvious the recited claim elements in claim 1, namely, a control unit (6), an analytical system (27), a sensor (28) for measuring cell concentration, an analyzer (41), a first regulator (42), and a first reference operator (43), wherein the cell-contaminated medium is removed from the bioreactor (1) to the second harvest receptacle (18) through the use of a harvest pump (20), wherein the harvest pump (20) and second harvest receptacle (18) are downstream of the bioreactor (1). Lucido does not disclose any method or device to remove cell concentration from the bioreactor to a second harvest receptacle. The only

disclosure is to a process that recites an "alarm is hooked up to a computer via telephone lines which relays the sounding of the alarm to a central station. At this station the problem can be assessed and a repair unit dispatched as needed". *See* Lucido at Col. 8, lines 36-40. This process is not equivalent to the measurement and control of cell concentration in the bioreactor as recited in claim 1 of the present invention, which requires each of elements (6), (27), (28), (41), (42), (43), (18) and (20).

Applicants submit that combining Lucido with the cited art would not yield the present invention, because the Examiner has not provided evidence in the cited art for a sensor for measuring cell concentration or the specific system for regulating the cell concentration as recited in claim 1 of the present application. Further, Applicants submit there is no disclosure of how to combine the computer controlled system of Gruenberg with the turbidity sensor of Lucido with a system the removes cell-contaminated medium via a downstream pump and harvest receptacle, because neither Gruenberg or Lucido teach a downstream pump connected to a harvest receptacle for cell-contaminated harvest or a procedure to automate the process based on the results of a turbidity sensor. Conjecture, speculation and the assumption of undisclosed elements plus a hypothetical combination of multiple unrelated references cannot be grounds for an obviousness rejection.

Furthermore, because Lucido is related to a process for removing industrial waste from sewage systems, Applicants submit that this is non-analogous art, and therefore would not be used by a person skilled in the art looking to add to the teachings of Major, Cornelissen and/or Gruenberg.

The Examiner has introduced new art, namely, Bartok, in the present Office Action to alleviate several of the deficiencies noted in Applicants Amendment dated August 10, 2009. The Examiner argues that Bartok renders obvious the use of the system for removing cell-contaminated medium recited in the present claims. Applicants submit that Bartok is not relevant to this system because the device in Bartok only contains a single harvest receptacle (5), which is employed for receiving "fermentation broth". *See* Bartok at Col. 1, lines 51-65, and Fig. 1. After removal of the "fermentation broth" from the fermentation vessel, the broth can be filtered by "sterile filters (16)" ***downstream*** of the single harvest receptacle (5). *See* Bartok at Col. 4, lines 56-67, and Fig. 1. There is no disclosure of a first harvest receptacle (16) for filtered permeate and a second harvest

receptacle (18) for a cell-contaminated product in Bartok, and therefore there can be no teaching with regard to removing cell-contaminated medium separately from filtered permeate as recited in the pending claims.

Applicants submit that if a person skilled in the art combined Bartok and Cornelissen the results would be a method and device which contained a single harvest receptacle, wherein the single harvest receptacle could be further filtered ***downstream*** of the harvest receptacle to remove additional waste. As with Cornelissen discussed above, Bartok teaches away from a method and device that separately removes filtered permeate and cell contaminated harvest, and provides different procedures for filtering and removing waste. Therefore a person skilled in the art would not seek to combine Major with either Cornelissen or Bartok. As discussed Bartok removes the entire filtration broth from the fermenter and then separately filters permeate downstream of the harvest receptacle, this is incompatible with the procedure disclosed in Major, wherein cell contaminated product is removed separately from filtered permeate.

Applicants submit the only way a person skilled in the art could combine Cornelissen, Bartok and Major and arrive at the present invention, would require the present specification as a roadmap. The disclosure in Major cannot simply be added to the disclosures in Bartok and Cornelissen. In contrast, Bartok and Cornelissen would have to be completely restructured to alter the process in which permeate is ultimately removed from the system to be compatible with a system as described in Major. The restructuring would essentially destroy the procedures and devices described in Bartok and Cornelissen. This restructuring is beyond a simple combination of known elements. Further, instructions on how to successfully construct and operate such a device can only be found in the present specification. The fact that the Examiner has been required to cite five unrelated prior art sources in an attempt to render obvious the present claims proves that this combination is not simple or obvious to one skilled in the art.

The remaining dependent claims 2-16 all incorporate each and every limitation of claim 1, and therefore are also not rendered obvious by the cited prior art.

Therefore because the cited prior art does not teach or suggest each and every element of claims 1-16, it is requested that the above §103(a) rejection be withdrawn.

In paragraphs 23-29 of the Office Action the Examiner rejected claims 17-19 under 35 U.S.C. §103(a) as being obvious over Cornelissen in view of Major and Gruenberg and further in view of Bartok.

Reconsideration is requested.

Claim 17 recites a device for biotechnologically producing valuable products using a system of feed receptacles, a bioreactor, pumps, a cross flow filtration unit and at least two harvest receptacles, one for storing filtered permeate and a second for removing cell-contaminated medium. Claim 17 further recites a device that measures the cell concentration of the bioreactor by use of a control unit (6), an analytical system (27), a sensor (28) for measuring cell concentration, an analyzer (41), a first regulator (42), and a first reference operator (43), and is capable of adjusting the cell concentration to a predetermined level by removing cell-contaminated medium from the bioreactor (1) to the second harvest receptacle (18) through the use of a harvest pump (20). Claim 17 further recites a second regulator (44) which receives a signal from a weighing device (22) which measures the weight of the bioreactor (1), and wherein said second regulator (44) compares the weight of said bioreactor (1) with a desired weight stored in a second reference operator (45), and based on the comparison of the measured weight and the desired weight, said second regulator (44) sends a control signal to an upstream feed pump (8), which in turn sends medium to the bioreactor (1) from an upstream medium containing feed receptacle (2).

In paragraph 27 of the Office Action the Examiner states that the system for measuring and readjusting nutrient medium in the bioreactor recited in claim 17 was rendered obvious by the disclosure in Cornelissen of a weighing device connected to the bioreactor shown in Figure 3 of Cornelissen. Applicants submit that the disclosure in Cornelissen does not teach the elements recited in claim 17. Specifically the weighing device in Cornelissen is connected to a pump on the ***downstream*** side of the bioreactor, wherein this ***downstream*** pump connects a product harvest receptacle and a microfiltration device, both of which are also on the ***downstream*** side of the bioreactor. This disclosure teaches away from the presently claimed invention where the weighing device is connected to an ***upstream*** feed pump connected to an ***upstream*** medium containing feed receptacle.

Additionally as discussed, the cited prior art, namely, Cornelissen, Major, Bartok and Gruenberg (and even Lucido, which has not been included in this rejection), does not teach or suggest each and every element of claim 17 of the present application. Specifically, the cited prior art does not teach the elements for measuring cell concentration (as opposed to weight or turbidity) in a bioreactor and the elements necessary for removing excess cell concentration from the bioreactor as recited in claim 17.

In paragraph 26 of the Office Action the Examiner states "the motor is connected to an analyzer, the control unit (Fig. 1) is connected to the process computer and would indicate changes within the bioreactor that would initiate the pump to withdraw product from the bioreactor". Applicants submit that this is conjecture based on Figure 1 and is not disclosed in the specification of Gruenberg. Additionally, there is no indication if cell-contaminated product or filtered permeate would be removed from the bioreactor by this hypothetical process. Applicants submit that this disclosure does not render obvious the system recited in claim 17, which measures cell concentration and actively removes only cell-contaminated product, not filtered permeate, from the bioreactor (1) via the downstream harvest pump and second harvest receptacle (18).

As discussed above, neither Bartok nor Cornelissen disclose a device which contains both a first and second harvest receptacle. Further, both Bartok and Cornelissen are incompatible with the device taught in Major because both references already disclose procedures for removing waste from their product receptacles, and therefore a person skilled in the art would not look to Major to alter the teachings in Bartok and Cornelissen. More specifically, a person skilled in the art could not combine Bartok, Cornelissen and Major and arrive at the present invention without the use of the present specification as a roadmap as discussed above in relation to claim 1.

The remaining dependent claims 18-19 all incorporate each and every limitation of claim 17, and therefore are also not rendered obvious by the cited prior art.

Therefore, it is requested that the §103(a) rejection with regard to claims 17-19 be withdrawn.

Based upon the above remarks, Applicants respectfully submit that claims 1-19 are allowable over the prior art and that the present application is in proper form for allowance.

Favorable consideration and early allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

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